

Tadalafil in patients with chronic obstructive pulmonary disease: a randomised, double-blind, parallel-group, placebo-controlled trial

Andrew R Goudie, Brian J Lipworth, Pippa J Hopkinson, Li Wei, Allan D Struthers



Summary

Background Phosphodiesterase-5 (PDE5) inhibitors improve exercise capacity and quality of life in patients with idiopathic pulmonary arterial hypertension. However, whether such beneficial effects take place in selected populations with chronic obstructive pulmonary disease (COPD) remains uncertain. We aimed to assess the effects of tadalafil—a PDE5 inhibitor—on exercise capacity and quality of life in patients with COPD and mild pulmonary hypertension.

Methods We did a randomised, double-blind, parallel-group, placebo-controlled trial at three centres in Scotland, UK, between Sept 1, 2010, and Sept 1, 2012. Patients with moderate to severe COPD were randomly assigned (1:1), via centralised randomisation with a computer-generated sequence and block sizes of four, to receive daily tadalafil 10 mg or placebo for 12 weeks. Patients, study investigators, outcome assessors, and those administering drugs were masked to group allocation. The primary endpoint was the mean placebo-corrected difference between the baseline and final 6 min walk distance after 12 weeks. We measured change in quality of life at baseline, 8 weeks, and 12 weeks, with standardised questionnaires. Analysis was per protocol and by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01197469.

Findings 120 patients were randomly assigned to receive tadalafil (n=60) or placebo (n=60), of whom 56 (93%) versus 57 (95%) completed the study. At 12 weeks the difference in 6 min walking distance between the tadalafil and placebo groups was 0·5 m (95% CI −11·6 to 12·5; p=0·937). We recorded no statistically significant changes in quality of life (between-group difference on the St George's Respiratory Questionnaire −2·64 [95% CI −6·43 to 1·15]; Research and Development version 1 short-form-36 4·08 [−1·35 to 9·52]; Minnesota Living with Heart Failure questionnaire −2·31 [−7·06 to 2·45]). 19 (32%) of 60 patients in the treatment group had dyspepsia; the severity of dyspepsia ranged from mild to severe, with four (21%) of 19 patients needing a proton-pump inhibitor. Five (8%) of 60 participants had dyspepsia in the placebo group. Headache was noted in 17 (28%) patients in the treatment group versus 5 (8%) in the placebo group, but was mild in all patients. Two (3%) patients in the treatment group had facial flushing, which resulted in one withdrawal. Other withdrawals within the tadalafil group happened after a transient ischaemic attack and two deaths (ruptured abdominal aortic aneurysm and pneumonia).

Interpretation Tadalafil does not improve exercise capacity or quality of life despite exerting pulmonary vasodilation.

Funding Chief Scientist Office for Scotland.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity worldwide. Pulmonary vascular disease happens early in the natural history of COPD, when pulmonary vascular changes have been reported in cigarette smokers with normal spirometry values.¹ Pulmonary arterial vasoconstriction, vessel-wall hypertrophy, and loss of pulmonary blood vessels contribute to the burden of pulmonary vascular disease, resulting in the development of pulmonary hypertension.

COPD-associated pulmonary hypertension reduces exercise tolerance² and quality of life. Modest increases in pulmonary arterial pressure, that are less than the cutoff considered to represent pulmonary hypertension, can strongly predict mortality³ and risk of hospital admission during an exacerbation.⁴ In patients with COPD without pulmonary hypertension (mean pulmonary artery

pressure <25 mm Hg), or with borderline hypertension (21–25 mm Hg), these slight changes in pulmonary arterial pressure are associated with impaired right ventricular systolic function, hypertrophy, and dilatation,⁵ changes that are increasingly present as the severity of pulmonary vascular disease worsens. Furthermore pulmonary arterial pressures frequently rise abnormally during activities of daily living, even in individuals without resting pulmonary hypertension.⁶ Although severe, or so-called disproportionate, pulmonary hypertension in patients with low-severity airway obstruction does take place in patients with COPD, it is uncommon (<5% prevalence),⁷ possibly representing the coexistence of idiopathic pulmonary arterial hypertension.

Phosphodiesterase-5 (PDE5) inhibitors are pulmonary arterial vasodilator drugs that are used to treat pulmonary hypertension, supported by evidence that they improve

Lancet Respir Med 2014;
2: 293–300

Published Online
March 5, 2014
[http://dx.doi.org/10.1016/S2213-2600\(14\)70013-X](http://dx.doi.org/10.1016/S2213-2600(14)70013-X)

See [Comment](#) page 254

Division of Cardiovascular
and Diabetes Medicine,
University of Dundee, Dundee,
Scotland, UK (A R Goudie MD,
Prof B J Lipworth MD,
P J Hopkinson, L Wei PhD,
Prof A D Struthers MD)

Correspondence to:
Dr Andrew R Goudie, University
of Dundee, Dundee DD1 9SY,
Scotland, UK
andrew.goudie@nhs.net

exercise capacity and quality of life.⁸ Although sildenafil—a short-acting PDE5 inhibitor—can improve pulmonary haemodynamics at rest and during exercise in patients with COPD-associated pulmonary hypertension,⁹ whether pulmonary arterial vasodilation improves exercise capacity and quality of life has not been established. Concerns about the potential for clinical worsening remain on the basis of the use of other

pulmonary vasodilator drugs, such as bosentan in unselected populations with severe COPD and sildenafil in patients with severe COPD with emphysema, but without pulmonary hypertension.^{10,11} In both studies, deleterious effects were reported on quality of life, with no beneficial effect on exercise capacity. We postulated that treatment with tadalafil—a long-acting PDE5 inhibitor—would improve exercise capacity and quality of life in selected patients with COPD and mild pulmonary hypertension.

Panel 1: Inclusion and exclusion criteria

Inclusion criteria

- Male or female participants, aged between 35 and 85 years inclusive
- Known diagnosis of chronic obstructive pulmonary disease
- A post-bronchodilator forced expiratory volume in 1 s <80% predicted
- Pulmonary acceleration time <120 ms or right ventricular systolic pressure >30 mm Hg

Exclusion criteria

- Pulmonary stenosis
- Left-ventricular outflow obstruction confirmed by echocardiography
- Left-ventricular systolic dysfunction (<45%)
- Patients taking nitrates, nicorandil, or doxazosin
- Systolic blood pressure <90 mm Hg, recent stroke, unstable angina, past history of non-arteritic anterior ischaemic optic neuropathy

Methods

Study design and patients

We undertook this randomised, double blind, parallel-group, placebo-controlled trial at three centres in Scotland, UK (Dundee, Perth, and Fife) between Sept 1, 2010, and Sept 1, 2012. We recruited patients with COPD via a network of pulmonary physiotherapists, respiratory consultants, and family doctors covering two UK National Health Service boards (Tayside and Fife) where potential candidates were identified through COPD databases.

Panel 1 shows the study eligibility criteria. All patients were smokers or ex-smokers with a diagnosis of COPD confirmed according to American Thoracic Society and European Respiratory Society criteria, a post-bronchodilator forced expiratory volume in 1 s (FEV₁) less than 80%, and an FEV₁ to forced vital capacity ratio of less than 70%.¹² The echocardiographic inclusion criteria signify values beyond the normal range (ie, pulmonary acceleration time <120 ms or right ventricular systolic pressure >30 mm Hg). Participants had had no exacerbation of COPD for at least 1 month at study entry. All regularly prescribed COPD drugs were continued. All patients provided written informed consent. Ethics approval was obtained from the North Research Ethics Committee (reference 10/S0801/46).

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio, via centralised randomisation with a computer-generated sequence and block sizes of four, to receive daily tadalafil 10 mg or matched placebo, orally. The intervention and placebo packs were identical in presentation (capsules and bottle) and double blinding was maintained throughout. Patients, study investigators, outcome assessors, and those administering drugs were masked to group allocation. Unmasking was done only after the end of the trial once all data had been collected and analysed.

Procedures

We used a MicroLoop spirometer to establish COPD diagnoses (Micro Medical, Rochester, UK). ARG undertook echocardiographs with a Philips iE33 system (Philips, The Netherlands) for participants from Dundee, and the Siemens Acuson CV70 (Siemens AG Medical

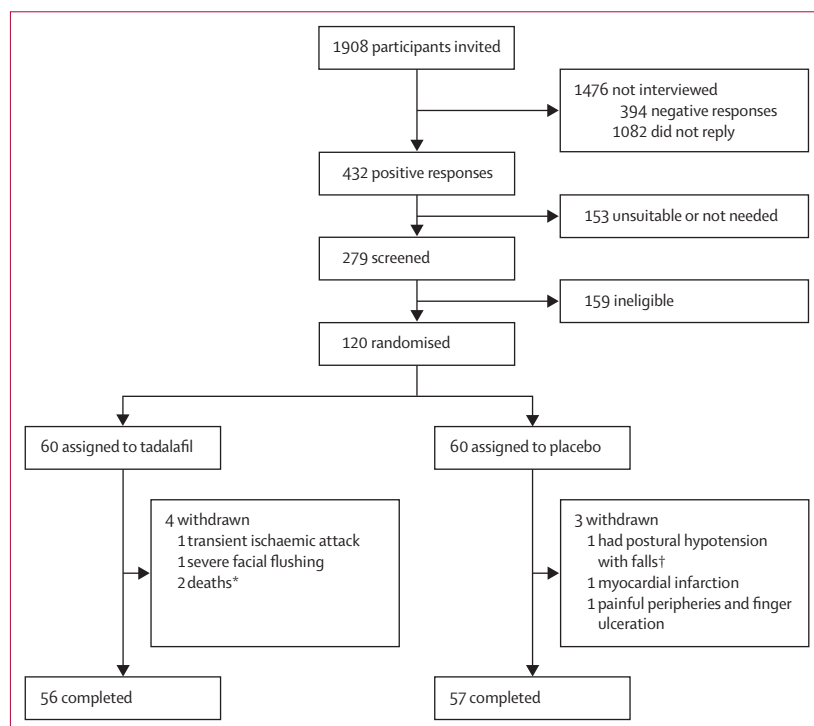


Figure 1: Trial profile

*Ruptured abdominal aortic aneurysm; ventilator-associated pneumonia after exacerbation of chronic obstructive pulmonary disease. †Admitted to hospital.

Solutions, Germany) for those from Perth and Fife. In addition to standard acoustic windows, we used an oblique subcostal window to assess the pulmonary acceleration time and the right-ventricular ejection time with pulse-wave Doppler, as previously described.¹³ We then calculated estimated mean pulmonary arterial pressure with the Dabestani equation,^{13,14} and right ventricular systolic pressure with the Bernoulli equation. We estimated right atrial pressure on the basis of the size and collapsibility of the inferior vena cava.¹⁵ We measured the thickness of the right ventricle (subcostal window acquisition) and the function (tricuspid annular plane systolic excursion) with a standard operating procedure.¹⁵ We qualitatively assessed the presence of dilatation of the right ventricle. Exercise capacity was limited by exertional breathlessness in all participants.

If eligibility criteria were met, patients were given a 50 mg test dose of sildenafil and observed for 3 h. Resting and postural blood pressure and pulse oximetry (SpO₂) were measured at baseline, and at 30, 60, 120, and 180 min. Participants were randomised if they were free from clinically significant symptoms, hypotension (systolic blood pressure <90 mm Hg) or symptomatic postural hypotension (a decrease of ≥20 mm Hg in systolic blood pressure drop during 3 min of standing) throughout the test dose observation period. Correspondence with family doctors, safety cards, and warning stickers on paper notes minimised the risk of clinically significant hypotension through inadvertent prescription of nitrate-containing drugs.

The 6 min walk test was done at baseline, and at weeks 8 and 12, on a flat, straight, 30 m course with use of standardised encouragement.¹⁶ Two walks were undertaken 1 h apart. Patients were allowed to use their usual walking aids but oxygen was not permitted. We assessed quality of life at baseline, 8 weeks, and 12 weeks with standardised questionnaires. The St George's Respiratory Questionnaire identifies how breathing problems affect patients' lives scored on a scale of 0 (no impairment) to 100 (maximum impairment). The Research and Development version 1 short-form-36 questionnaire measures functional health and well-being scores within 8 domains, scored from 0 to 100 whereby higher scores represent better function. The Minnesota Living with Heart Failure questionnaire has been validated for pulmonary hypertension¹⁷ whereby higher scores reflect worse quality of life. We measured SpO₂ at the beginning and end of the walk test and at any temporary stops that were needed because of severe exertional dyspnoea. B-natriuretic peptide, high-sensitivity C-reactive protein, and spirometry were also measured at baseline, and at weeks 8 and 12. The single-breath diffusing capacity of the lung was done in accordance with the American Thoracic Society and European Respiratory Society task force guidelines¹⁸ at baseline and 12 weeks (SensorMedics Vmax 229, SensorMedics Corporation, USA [Dundee and Perth];

	Tadalafil (n=60)	Placebo (n=60)
Age (years)	68 (8)	70 (7)
Men	42 (70%)	40 (67%)
BMI (kg/m ²)	26.7 (5.3)	25.7 (5.1)
MRC dyspnoea scale	3.4 (0.9)	3.4 (1.0)
Pack-year history	49.7 (23.0)	47.3 (18.8)
BODE index	4.4 (2.3)	4.3 (2.5)
FEV ₁ (L)*†	1.1 (0.4)	1.0 (0.5)
FEV ₁ (%)*†	41 (14.0)	40 (17.0)
Pulmonary acceleration time (ms)	98 (10.0)	97 (13.0)
Mean pulmonary arterial pressure (mm Hg)‡	30 (5.0)	31 (7.0)
Right ventricular systolic pressure (mm Hg)	42 (9.0)	42 (10.0)
SpO ₂	95.4 (3.0)	95.3 (2.8)
B-natriuretic peptide (pg/mL)	19.6 (9–46)	24.5 (12–50)
hs-CRP (mg/L)	2.92 (1.46–4.98)	2.64 (1.31–5.47)
Adjusted DLCO (%)*	40.9% (14.4)	34.7% (12.0)
Baseline 6MWD (m)	354 (105)	341 (104)
Bicarbonate (mmol/L)	26.6 (0.4)	26.7 (0.4)
Right ventricular hypertrophy (mm)	6.6 (0.2)	6.5 (0.2)
Right ventricular dilatation	17 (28%)	17 (28%)
TAPSE (mm)	22 (4.0)	21 (4.0)
Diabetes mellitus	3 (5%)	7 (12%)
Ischaemic heart disease	4 (7%)	5 (8%)
Cerebrovascular disease	7 (12%)	2 (3%)
Chronic kidney disease	7 (12%)	4 (7%)

Data are mean (SD), n (%), or median (IQR), unless otherwise indicated. BMI=body-mass index. MRC=modified research council. FEV₁=forced expiratory volume in 1 sec. SpO₂=blood oxygen saturation. hs-CRP=high-sensitivity C-reactive protein. DLCO=diffusion of lung carbon monoxide. 6MWD=6 min walking distance. TAPSE=tricuspid annular plane systolic excursion. *Litres and percentage predicted. †Post-bronchodilator. ‡Dabestani equation.

Table 1: Baseline characteristics

Morgan Pulmolab TT 501, Morgan Medical Ltd, UK [Fife]). Echocardiography was done at baseline and 12 weeks. Two additional safety visits and telephone consultations were organised around the main visits. Adverse events were logged and capsules were counted at all visits to assess compliance. Blood pressure and SpO₂ were measured at all visits.

Outcomes

The primary outcome was the mean placebo-corrected difference between the baseline and final 6 min walk distance after 12 weeks of tadalafil. Secondary measures were change in quality of life, cardiac stress (B-natriuretic peptide), systemic inflammation (high-sensitivity C-reactive protein), lung diffusion (single-breath diffusing capacity), lung function (spirometry), and cardiac function (echocardiography).

Statistical analysis

The primary objective was to establish whether tadalafil would improve exercise capacity in patients with COPD. Other work in this specialty suggests that a 54 m increase in 6 min walking distance should be regarded as the minimum clinically important distance at which patients

consider themselves to feel subjectively better.¹⁹ From the available literature we ascertained that a mean 6 min walking distance in patients with severe COPD would be roughly 285 m (SD 96).²⁰ A sample size of 104 patients was needed to achieve 80% power at a 5% significance level. We increased the number to 120 to account for dropouts. We present data as means with SDs for continuous variables, and as numbers with percentages for categorical variables. For the primary outcome, we analysed data with the student's *t* test to identify the mean difference between groups at 12 weeks. Furthermore, a general linear model with repeated measures for multiple time points (ANOVA) was done with a post-hoc Bonferroni correction to avoid confounding of the

overall α error in the two groups. We used a paired *t* test to test the differences within groups in data at baseline and 12 weeks. For the secondary outcome, we used the student's *t* test to examine the differences between the two groups. For non-normally distributed data we used the Mann-Whitney *U* test. We used the χ^2 test to assess the differences in categorical variables between the two groups. Primary analysis was per protocol, with a separate intention-to-treat analysis done with multiple imputation to address missing data.

No interim analysis was done. Analysis was done mainly on completers, with additional sensitivity analysis, and used data for the best walk test for each patient. Data analysis was independently verified by the study statistician. This trial is registered with ClinicalTrials.gov, number NCT01197469.

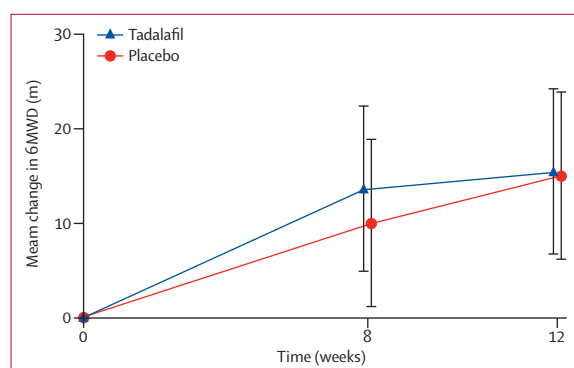


Figure 2: Mean change in 6MWD between groups over time
Error bars 95% CIs. 6MWD=6 min walking distance.

Role of the funding source

The Chief Scientist Office for Scotland (CZB/4/666) solely funded the study, with no role in the writing and final decision to submit for publication. Our sponsor was the University of Dundee who had no role in study design, data collection, data analysis, data interpretation, or writing of the report. ARG and PJH had full access to the all the data in the study and ARG had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 120 patients were randomly assigned to receive tadalafil (n=60) or placebo (n=60), of whom 113 (94%) completed the study. Baseline characteristics were similar between groups (table 1). Patients had severe COPD and borderline to mild pulmonary hypertension with a moderate impairment of diffusion capacity (table 1). The upper range for right ventricular systolic pressure was 81 mm Hg and the lower range for pulmonary acceleration time was 69 ms (estimated mean pulmonary arterial pressure 47 mm Hg). Right ventricular thickness was measurable at baseline in 114 (95%) of 120 patients. 108 (90%) patients had echocardiographic evidence of right ventricular hypertrophy (≥ 5 mm right ventricular free wall thickness). In the 89 patients in whom tricuspid annular plane systolic excursion could be measured, 86 (97%) had preserved right ventricular function. The high proportion of patients prescribed combination inhaled corticosteroid and long-acting β agonists (109 [91%]) and long-acting muscarinic antagonists (104 [87%]) was typical of a moderate to severe cohort with COPD. 13 (11%) patients were receiving long-term oxygen therapy and 16 (13%) were receiving a loop diuretic. 79 (66%) patients had exercise desaturation ($\geq 4\%$ decrease in SpO_2). No patients had a history of thromboembolic disease or were receiving anticoagulants.

In the per-protocol analysis, the placebo-corrected difference in 6 min walking distance after 12 weeks of tadalafil was 0.5 m (95% CI -11.6 to 12.5; $p=0.937$

	Tadalafil (n=56)	Placebo (n=57)	Absolute difference	p value
SGRQ*				
Total score	-1.00 (-3.57 to 1.56)	1.64 (-1.20 to 4.48)	-2.64 (-6.43 to 1.15)	0.170
Symptoms score	1.76 (-3.00 to 6.51)	-1.64 (-8.09 to 4.81)	3.40 (-4.54 to 11.33)	0.398
Activity score	-1.87 (-5.38 to 1.64)	2.54 (-0.80 to 5.88)	-4.41 (-9.20 to 0.38)	0.071
Impacts score†	-1.39 (-4.20 to 1.42)	2.12 (-1.01 to 5.25)	-3.51 (-7.68 to 0.66)	0.098
SF-36‡				
Physical functioning	2.68 (-1.36 to 6.72)	-1.40 (-5.14 to 2.33)	4.08 (-1.35 to 9.52)	0.139
Pain	0 (-10 to 10)	0 (-16.25 to 16.25)	..	0.365
General health	0 (-5 to 5)	0 (-7.5 to 7.5)	..	0.559
Emotional well-being	0 (-4 to 8)	0 (-10 to 8)	..	0.233
Physical role limitations	0 (0 to 0)	0 (-0 to 12.5)	..	0.775
Emotional role limitations	0 (0 to 0)	0 (0 to 0)	..	0.931
Social functioning	0 (-12.5 to 12.5)	0 (-12.5 to 12.5)	..	0.997
Energy or fatigue	0 (-10 to 10)	0 (-10 to 10)	..	0.577
MLHFQ*				
Total	-0.57 (-3.18 to 2.03)	1.74 (-2.28 to 5.75)	-2.31 (-7.06 to 2.45)	0.338
Physical	-0.14 (-1.68 to 1.39)	0.61 (-1.21 to 2.43)	-0.76 (-3.12 to 1.60)	0.527
Emotional	-0.39 (-1.09 to 0.31)	0.30 (-1.17 to 1.77)	-0.69 (-2.31 to 0.93)	0.398

Data are mean (95% CI) or median (IQR), unless otherwise indicated. SGRQ=St George's Respiratory Questionnaire. SF-36=Short Form (36) Health Survey (RAND version 1). MLHFQ=Minnesota Living with Heart Failure Questionnaire. *Negative scores show improvement in quality of life. †Social function ‡Higher score reflects better quality of life.

Table 2: Mean change in quality-of-life scores at 12 weeks compared with baseline

	Tadalafil (n=56)			Placebo (n=57)			Mean difference between groups (95% CI)	p value*
	n (%)	Initial	Final	n (%)	Initial	Final		
PAT (ms)	55 (98%)	97.7 (9.9)	106.3 (12.8)	56 (98%)	97.0 (12.9)	98.3 (15.8)	7.3 (0.9 to 13.6)	0.001
mPAP (mm Hg)†	55 (98%)	30.1 (5.2)	26.6 (5.2)	56 (98%)	30.8 (6.8)	30.8 (7.5)	-3.5 (-6.6 to -0.4)	0.025
PAT/RVET	55 (98%)	0.36 (0.08)	0.39 (0.05)	56 (98%)	0.37 (0.06)	0.37 (0.06)	0.02 (0.01 to 0.04)	0.008
RVSP (mm Hg)	12 (21%)	43.5 (9.5)	38.8 (10.3)	13 (23%)	43.9 (10.9)	51.5 (15.6)	-12.3 (-20.9 to -3.6)	0.007
TAPSE (mm)	37 (66%)	21.3 (3.7)	22.1 (4.1)	36 (63%)	21.1 (3.5)	20.8 (4.4)	1.1 (-1.1 to 3.3)	0.319

Data are mean (SD), unless otherwise indicated. PAT=pulmonary acceleration time. mPAP=mean pulmonary arterial pressure. PAT/RVET=ratio of pulmonary acceleration time to right ventricular ejection time. RVSP=right ventricular systolic pressure. TAPSE=tricuspid annular plane systolic excursion. *From two independent samples t tests. †Derived, based on Dabestani's equation.

Table 3: Echocardiographic parameters after 12 weeks by treatment group

	Tadalafil (n=56)			Placebo (n=57)			Mean difference between groups (95% CI)	p value*
	n (%)	Initial	Final	n (%)	Initial	Final		
B-natriuretic peptide (pg/mL)†	56 (100%)	1.29 (0.42)	1.32 (0.45)	57 (100%)	1.42 (0.44)	1.44 (0.48)	0.01 (-0.09 to 0.12)	0.844
hs-CRP (mg/L)†	56 (100%)	0.49 (0.47)	0.58 (0.52)	57 (100%)	0.47 (0.43)	0.53 (0.49)	0.03 (-0.12 to 0.18)	0.722
Adjusted DLCO (%)‡	56 (100%)	40.9 (15.2)	41.2 (16.4)	56 (98%)	35.1 (12.1)	34.2 (11.2)	0.85 (-1.46 to 3.16)	0.469
FEV ₁ (L)	56 (100%)	1.08 (0.38)	1.05 (0.38)	57 (100%)	1.01 (0.43)	0.99 (0.40)	-0.02 (-0.07 to 0.03)	0.420
FEV ₁ (%)§	56 (100%)	41.4 (14.7)	40.1 (15.4)	57 (100%)	39.5 (16.2)	38.9 (15.2)	-0.50 (-2.5 to 1.5)	0.615
Forced vital capacity (L)	56 (100%)	2.88 (0.8)	2.86 (0.77)	57 (100%)	2.74 (0.99)	2.82 (0.99)	0.22 (-0.42 to 0.85)	0.502
Forced vital capacity (%)§	56 (100%)	85.6 (18.4)	85.4 (19.9)	57 (100%)	83.5 (23.6)	84.9 (22.5)	-2.4 (-6.5 to 1.7)	0.250

Data are mean (SD), unless otherwise indicated. hs-CRP=high-sensitivity C-reactive protein. DLCO=diffusion capacity of lung for carbon monoxide. FEV₁=forced expiratory volume in 1 s. *From two independent samples t tests. †Log₁₀ for parametric testing; ‡Adjusted for haemoglobin, expressed as percentage of predicted value. §Percentage predicted.

Table 4: Secondary outcomes before and after 12 weeks of treatment by group

(figure 2). In the intention-to-treat population the difference was -1.3 m (-6.2 to 3.6; p=0.595). The adjusted analysis for baseline walking distance (ANCOVA) was 0.5 m (-11.7 to 12.6; p=0.934). We noted significant mean changes of 15.5 m (6.8–24.2; p=0.0007) in the tadalafil group and 15.0 m (6.5–23.6; p=0.0009) in the placebo group after 12 weeks compared with at baseline. Repeated measures ANOVA confirmed significant differences over time in both the tadalafil (p=0.001) and placebo groups (p=0.003). In a prespecified analysis, we analysed good walkers (≥ 285 m; n=88) and poor walkers (<285 m; n=23) separately. No significant differences in 6 min walking distance were shown between groups during the 12 weeks in both good walkers (mean difference -0.2 m, 95% CI -13.5 to 13.1; p=0.978) and poor walkers (7.5 m, -23.6 to 38.5; p=0.623). Furthermore, no significant changes were shown in the degree of exertional breathlessness during the 6 min walking test (p=0.714; data not shown). Conclusions were unchanged in further sensitivity analysis in patients with right-ventricular dilatation

(n=26, mean difference 20.5 m, 95% CI -10.4 to 51.4; p=0.184), the lowest (worst) pulmonary acceleration times (n=60, -6.0 m, -24.2 to 12.1; p=0.507), and the highest FEV₁ at baseline (n=58, 1.0 m, -16.5 to 18.6; p=0.905).

We recorded no statistically significant changes in any of the quality-of-life measures (table 2).

Table 3 provides echocardiographic data. On the basis of the mean pulmonary arterial pressure derived from pulmonary acceleration time, 114 (96%) of patients had a pressure of more than 20 mm Hg and 94 (79%) had a pressure of more than 25 mm Hg. We measured tricuspid annular plane systolic excursion in all patients when technically feasible (n=73). Data for right ventricular systolic pressure were limited to 25 patients in whom such data could be measured at both the start and the end of study. No statistically significant changes were noted in spirometry, diffusing capacity of the lung, B-natriuretic peptide, or high-sensitivity C-reactive protein (table 4). At 12 weeks, 49 (41%) patients had had an exacerbation of COPD. The frequency of exacerbations

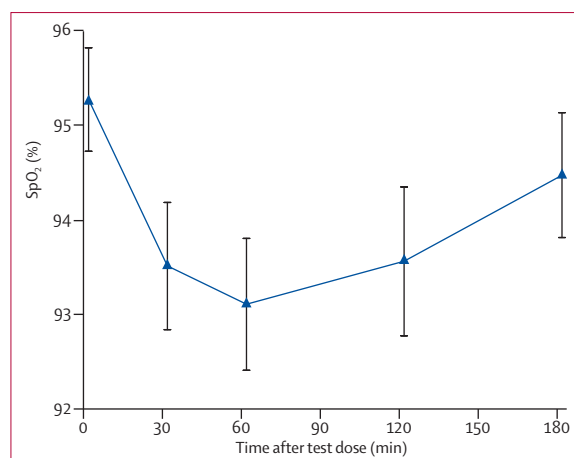


Figure 3: Effects of one 50 mg dose of sildenafil on SpO₂ over time
n=120. SpO₂=peripheral oxygen saturations.

was higher in patients in the placebo group than in those in the tadalafil group (27 [45%] vs 22 [37%]; $p=0.609$). Four (7%) patients in the placebo group were admitted to hospital during an exacerbation of COPD versus three (5%) patients in the treatment group.

Compliance was high (107 [95%] of 113 completers). Common side-effects of tadalafil were reported (data not shown). With the exception of dyspepsia and headache, all side-effects were transient in nature (data not shown). 19 (32%) of 60 patients in the tadalafil group had dyspepsia compared with five (8%) of 60 patients in the placebo group. The severity of dyspepsia ranged from mild to severe with four (21%) of 19 patients needing a proton-pump inhibitor. Headache was noted in 17 (28%) patients in the tadalafil group versus five (8%) in the placebo group, but was mild in all patients (data not shown). Two (3%) patients in the tadalafil group had facial flushing, which resulted in one withdrawal. Other withdrawals within the tadalafil group happened after a transient ischaemic attack and two deaths (ruptured abdominal aortic aneurysm and pneumonia).

After one 50 mg dose of oral sildenafil we noted a significant reduction in resting SpO₂ of 2.2% (95% CI 1.6–2.7; $p<0.0001$; figure 3). Despite this decrease, only one patient described a transient increase in breathlessness versus two patients who felt less breathless. 60 min after receiving the sildenafil, the mean systolic blood pressure reduced maximally by 15.6 mm Hg (11.1–20.0; $p<0.0001$). Five patients had symptomatic postural hypotension during the test dose and were therefore ineligible for randomisation. Chronic dosing with tadalafil at 10 mg once daily did not result in any significant differences between group in SpO₂ at 12 weeks, with a mean change of -0.91% (SD 1.6) in the tadalafil group and -0.70% (2.0) in the placebo group ($p=0.543$). We recorded no significant group differences in blood pressure (data not shown).

No patients receiving long-term oxygen therapy needed an increase in oxygen dose and no new prescriptions of oxygen therapy were reported during the trial period (data not shown).

Discussion

Use of tadalafil for 12 weeks did not improve exercise capacity, as measured by the 6 min walking distance. One possible explanation for this absence of effect is that in the presence of mild pulmonary hypertension, exercise capacity is mainly limited by exhaustion of the ventilatory reserve.^{21,22} Of our three chosen quality-of-life measures, the St George's Respiratory Questionnaire is the most relevant. We did not see an improvement in quality of life with 12 weeks of tadalafil treatment. The changes between groups in the activity and impacts score subdomains could mean that tadalafil might improve quality of life in a much larger study. However, if such an effect was not apparent in the 113 patients in our study, the clinical relevance of any change in quality of life is questionable.

Tadalafil doses higher than 10 mg might be more effective. At the time of our study design, tadalafil had not been licensed for pulmonary hypertension at the present daily 40 mg dose that has since become the accepted starting dose for patients with idiopathic pulmonary arterial hypertension.⁸ Our dose selection was informed by the anticipated pharmacokinetics in our elderly population by contrast with those in younger patients with idiopathic pulmonary arterial hypertension. The half-life of tadalafil is increased (from 17.5 to 21.6 h) and clearance is also significantly reduced in elderly people.^{23,24} Information from the Electronic Medicines Compendium states that a dose adjustment in elderly patients is not warranted; however, this recommendation is based on data in healthy patients and not in those with severe COPD and pulmonary vascular disease—a largely unstudied population. In the absence of any data about the use of daily dosing with tadalafil in pulmonary hypertension, we drew inspiration from the successful treatment of erectile dysfunction, for which comparatively low single doses of tadalafil are used and daily dosing with 10 mg or above was not recommended. Furthermore in the pivotal randomised trial by Galiè and colleagues,⁸ 10 mg, 20 mg, and 40 mg dosing of tadalafil at 12 weeks seemed to be equally effective for improvement of 6 min walking distance, although only the 40 mg dose was associated with a significant increase in walking distance and prolonged time to clinical worsening at 16 weeks. By contrast with our own treatment-naïve study population, more than 50% of the patients in Galiè and colleagues' trial were receiving bosentan, which because of interaction with cytochrome P450 3A4 could necessitate high doses to be effective. Our chosen dose (10 mg) of tadalafil caused the expected pulmonary vasodilatation with no effect on 6 min walking distance.

We noted significant increases in pulmonary acceleration time in patients in the treatment group, only

in keeping with a small reduction in pulmonary vascular resistance and pulmonary pressure, the latter of which we estimated to be 3·5 mm Hg.^{13,25} This finding supports those from other published work showing that after 3 months of sildenafil, the pulmonary acceleration time was the only echocardiographic parameter to change significantly in line with other well-established right-heart catheter measures (mean pulmonary artery pressure and pulmonary vascular resistance).²⁶ Acute sildenafil dosing decreased SpO₂ on the basis of ventilation perfusion mismatch, which increased blood flow to poorly ventilated areas of the lung through release of hypoxic pulmonary vasoconstriction. This event was not apparent during chronic dosing with tadalafil despite evidence of pulmonary vasodilatation, possibly because of adaptive processes with chronic dosing, mitigating any regional ventilation perfusion mismatching.

One perceived limitation of our study is our considered decision to not undertake right-heart catheterisation for patient selection and assessment of treatment response. We ruled out right-heart catheterisation for both logistical (distance of travel for patients and need for hospital admission) and ethical reasons, in that repeated catheterisation poses a small but unacceptable risk to patients, particularly because consideration of catheterisation is not routine practice in patients with COPD with suspected borderline or mild pulmonary hypertension. Although other studies in this specialty have suggested use of pulmonary vasodilator drugs on the basis of the high prevalence of exercise-induced pulmonary hypertension in patients with severe COPD, we wished to further characterise our participants with echocardiography.^{10,11} Almost all the participants in our study had a measurable pulmonary acceleration time; as such, acceleration time is the key echocardiography parameter defining our cohort. Echocardiography-derived pulmonary acceleration time and pulmonary acceleration time to right ventricular ejection time ratio have an excellent correlation ($r=0\cdot88$ to $-0\cdot90$) with right catheter-derived mean pulmonary arterial pressure.^{13,27} This technique is advantageous in the assessment of patients with pulmonary hypertension who are poorly echogenic, particularly when the discordance between right ventricular systolic pressure and invasive catheter measures is considered.²⁸ Although a precise estimation of mean pulmonary arterial pressure cannot be derived from pulmonary acceleration time, our methods were chosen to be a simple, reliable way to stratify participants. Use of all available echocardiographic methods and not solely the right ventricular systolic pressure has been emphasised in a debate of pros and cons.²⁹

Another potential limitation is our use of fairly modest indicators of pulmonary vascular disease for assessment of inclusion in the study, at the risk of including patients without pulmonary hypertension. Even mild increases in pulmonary pressure, not presently considered to represent pulmonary hypertension, can result in clinically

Panel 2: Research in context

Systematic review

We searched PubMed between Jan 1, 1980, and Jan 1, 2014, for “phosphodiesterase-5 inhibitors”, “tadalafil”, “sildenafil”, “COPD”, “pulmonary hypertension”, “pulmonary arterial hypertension”, “exercise tolerance”, and “exercise capacity”. Our review of the existing literature emphasised the scarcity of robust evidence for or against the use of phosphodiesterase-5 (PDE5) inhibitors in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease (COPD). We identified only two randomised trials. In the first,¹¹ in patients with COPD and emphysema, but without pulmonary hypertension, sildenafil had no effect on exercise capacity and worsened quality of life. The second trial³⁰ showed that sildenafil in addition to pulmonary rehabilitation did not confer an additional improvement in exercise tolerance in patients with severe COPD and mild to moderate pulmonary hypertension.

Interpretation

Our findings suggest that in patients with moderate to severe COPD, selected to have borderline to mild pulmonary hypertension, tadalafil does not improve exercise capacity or quality of life. This outcome is in keeping with evidence from randomised trials suggesting that in patients with COPD with emphysema and no pulmonary hypertension, or in those with COPD and mild to moderate pulmonary hypertension undertaking pulmonary rehabilitation, sildenafil does not improve exercise capacity or quality of life. Our findings therefore discourage use of PDE5 inhibitors in patients with moderate to severe COPD and borderline to mild pulmonary hypertension as a means to improve exercise capacity and quality of life. Further trials should focus on comparatively rare subgroups such as individuals with severe pulmonary hypertension or mild airflow obstruction, whereby PDE5 inhibitors could still conceivably have beneficial effects.

significant changes to the structure and function of the right heart.⁵ Our selection criteria of a pulmonary acceleration time less than 120 ms was chosen to include all patients with a mean pulmonary arterial pressure of greater than 16 mm Hg. The estimated mean pulmonary arterial pressure in our final cohort and the proportion of patients with right-ventricular dilation are consistent with a degree of pulmonary vascular disease. Although the upper range for right ventricular systolic pressure and the lower range for pulmonary acceleration time suggest the inclusion of those with severe pulmonary hypertension, small numbers preclude any conclusions about the effectiveness of tadalafil in participants with more severe pulmonary hypertension. Tadalafil could still conceivably improve exercise capacity in individuals with more severe pulmonary hypertension or mild airflow obstruction—a comparatively rare subgroup in whom further study is warranted.

Most studies of COPD that include measures of right-heart catheterisation naturally represent highly selected groups of patients with COPD who are referred to tertiary centres for consideration of lung transplant, surgery for reduction of lung volume, or investigation of disproportionate or severe pulmonary hypertension. In our cohort, the lack of clinical improvement with tadalafil, despite enrichment of the study population through echocardiography, suggests that PDE5 inhibitors do not improve exercise capacity and quality of life in patients with moderate to severe COPD, even if there is a

suggestion of pulmonary hypertension on echocardiography. This message is timely because sildenafil is no longer patented and is available on a generic tariff. Our findings are consistent with the work of Blanco and colleagues³⁰ in which sildenafil did not further improve exercise capacity in participants undergoing pulmonary rehabilitation, based on a cohort with echocardiography-defined pulmonary hypertension and, to a lesser extent, hypertension confirmed by right-heart catheterisation. Our study differs in its primary assessment of exercise capacity and has been powered accordingly, necessitating double the participants. Our complementary findings strengthen the case against the indiscriminate use of PDE5 inhibitors in COPD patients with borderline or mild pulmonary hypertension (panel 2).

In what represents a large cohort of patients with COPD and mild pulmonary hypertension we have shown that tadalafil at a dose of 10 mg per day does not improve exercise capacity despite exerting its pharmacological effect of pulmonary vasodilation.

Contributors

ARG is the guarantor of contents and contributed to design, data acquisition, analysis, interpretation, and drafting of the manuscript. BJL contributed to the study conception, design, and revision of the manuscript. PJH contributed to the data acquisition and manuscript revision. LW contributed to the conception, design, analysis, interpretation, revision of article, and is the study statistician. ADS contributed to the conception, design, and revision of the manuscript.

Declaration of interests

We declare that we have no competing interests.

Acknowledgements

We thank the Chief Scientist Office for Scotland (CZB/4/666), who funded this study.

References

- Santos S, Peinado VI, Ramirez J, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *Eur Respir J* 2002; **19**: 632–38.
- Sims MW, Margolis DJ, Localio AR, Panettieri RA, Kawut SM, Christie JD. Impact of pulmonary artery pressure on exercise function in severe COPD. *Chest* 2009; **136**: 412–19.
- Weitzenblum E, Hirth C, Ducolone A, Mirhom R, Rasaholjanahary J, Ehrhart M. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 1981; **36**: 752–58.
- Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **159**: 158–64.
- Hilde JM, Skjorten I, Grotta OJ, et al. Right ventricular dysfunction and remodeling in COPD without pulmonary hypertension. *J Am Coll Cardiol* 2013; **62**: 1103–11.
- Christensen CC, Ryg MS, Edvardsen A, Skjongsberg OH. Relationship between exercise desaturation and pulmonary haemodynamics in COPD patients. *Eur Respir J* 2004; **24**: 580–86.
- Chaouat A, Bugnet A-S, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; **172**: 189–94.
- Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; **119**: 2894–903.
- Blanco I, Gimeno E, Munoz PA, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am J Respir Crit Care Med* 2010; **181**: 270–78.
- Stolz D, Rasch H, Linka A, et al. A randomised, controlled trial of bosentan in severe COPD. *Eur Respir J* 2008; **32**: 619–28.
- Lederer DJ, Bartels MN, Schluger NW, et al. Sildenafil for chronic obstructive pulmonary disease: a randomized crossover trial. *COPD* 2012; **9**: 268–75.
- Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; **23**: 932–46.
- Kiely DG, Cargill RI, Wheeldon NM, Coutie WJ, Lipworth BJ. Haemodynamic and endocrine effects of type 1 angiotensin II receptor blockade in patients with hypoxaemic cor pulmonale. *Cardiovasc Res* 1997; **33**: 201–08.
- Dabestani A, Mahan G, Gardin JM, et al. Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography. *Am J Cardiol* 1987; **59**: 662–68.
- Howard LS, Grapsa J, Dawson D, et al. Echocardiographic assessment of pulmonary hypertension: standard operating procedure. *Eur Respir Rev* 2012; **21**: 239–48.
- ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166**: 111–17.
- Cenedese E, Speich R, Dorschner L, et al. Measurement of quality of life in pulmonary hypertension and its significance. *Eur Respir J* 2006; **28**: 808–15.
- MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; **26**: 720–35.
- Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997; **155**: 1278–82.
- Criner GJ, Cordova FC, Furukawa S, et al. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **160**: 2018–27.
- Pynnaert C, Lamotte M, Naeije R. Aerobic exercise capacity in COPD patients with and without pulmonary hypertension. *Respir Med* 2010; **104**: 121–26.
- Naeije R, Boerrigter BG. Pulmonary hypertension at exercise in COPD: does it matter? *Eur Respir J* 2013; **41**: 1002–04.
- Francis S, Corbin J. Molecular mechanisms and pharmacokinetics of phosphodiesterase-5 antagonists. *Curr Urol Rep* 2003; **4**: 457–65.
- Forgue ST, Patterson BE, Bedding AW, et al. Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2006; **61**: 280–88.
- Tossavainen E, Soderberg S, Gronlund C, Gonzalez M, Henein MY, Lindqvist P. Pulmonary artery acceleration time in identifying pulmonary hypertension patients with raised pulmonary vascular resistance. *Eur Heart J Cardiovasc Imaging* 2013; **7**: 7.
- Mikhail GW, Prasad SK, Li W, et al. Clinical and haemodynamic effects of sildenafil in pulmonary hypertension: acute and mid-term effects. *Eur Heart J* 2004; **25**: 431–36.
- Kitabatake A, Inoue M, Asao M, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation* 1983; **68**: 302–09.
- Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003; **167**: 735–40.
- Paterson I, Michelakis ED. The role of doppler echocardiography in pulmonary artery hypertension: the importance of proving the obvious. *Chest* 2011; **139**: 973–75.
- Blanco I, Santos S, Gea J, et al. Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. *Eur Respir J* 2013; **42**: 982–92.